

Emerging treatments for age-related macular degeneration

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Abstract.

Management of age-related macular degeneration (AMD) is a growing public health challenge worldwide. At present, anti-VEGF injections offer exceptional visual outcomes for neovascular AMD (nvAMD) compared to prior options. Many new avenues of treatment are under investigation for both nvAMD and dry AMD, and this narrative review summarises emerging developments, in the process illustrating the nature of the data collected prior to interventions becoming available in our practices. For nvAMD, encouraging phase II trial results were seen with pegpleranib, an antibody against platelet derived growth factor, but phase III results failed to show effectiveness, and have been terminated. Also under investigation for nvAMD are anti-angiopoietin antibodies, anti-VEGF-C and -D antibodies, ‘DARPin’ and even topical treatments. Novel means of delivering drug to the retina may also prove fruitful: a trial of a reservoir port is described. There is no medical treatment currently for atrophic AMD, but this may soon change. While visual cycle slowing may not have lived up to the initial hope of its usefulness, complement inhibition may do so, and may be particularly effective in those of a specific genetic subgroup. Epiretinal and other retinal implants will have a place for some patients. The potential for stem cell-based treatment offers great hope, though much work remains to be done and several trials are ongoing. In the next five years, a range of clinical trial results will emerge which may transform once again how we approach AMD, and hopefully improve outcomes for our patients.

Summary.

The management of AMD underwent a paradigm shift with the advent of anti-VEGFs as treatment and of OCT to monitor the condition. Presently there are several interesting new management options on the horizon for both neovascular and atrophic AMD. This narrative review summarises emerging interventions that may be mentioned in popular and professional press, and may be on our menu of treatment options to discuss with patients in the near future.

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Introduction.

When optometry and medical students are taught at university, a dramatic caveat should be added to much of what they learn: that it will be of no use in their careers to come. Knowledge is constantly replaced or updated, and clinical skills are at risk of being superseded by technology: for example the time-honoured art of direct ophthalmoscopy may be on the verge of redundancy (Purbrick and Chong 2015). Age-related macular degeneration (AMD) is the commonest cause of visual impairment in the Western world, and is becoming an increasing public health challenge in Asia (Velez-Montoya *et al.* 2014). The management of AMD underwent a paradigm shift in 2006 with the advent of anti-vascular endothelial growth factor treatments (anti-VEGFs) and optical coherence tomography (OCT).

It should be remembered that VEGF exists for a reason: it has a physiological role in supporting vascular homeostasis. Animal models have compared the retinas of mice genetically engineered to lack soluble VEGF with the retinas of wild type mice *with* soluble VEGF (Saint-Geniez, Kurihara *et al.* 2009). The VEGF-deficient mice have shown severe disruption of choriocapillaris, retinal pigmented epithelial (RPE) and the neural retina. However *excessive* VEGF has been implicated in the development of macular oedema and neovascularization. Anti-VEGFs such as ranibizumab and aflibercept are licensed in the UK for management of neovascular (or 'wet') AMD (nvAMD), and for macular oedema secondary to diabetic maculopathy or retinal vein occlusion (Hirani S 2017). Compared to previous management options, replicated high quality evidence has shown them to be exceptionally effective in nvAMD in improving functional outcomes, like best corrected visual acuity (BCVA) and anatomical outcomes, like retinal thickness on OCT and leakage on fundus fluorescein angiography (FFA). They have improved the visual prospects of countless people, and have been credited with reductions in blindness registrations due to AMD (Borooah, Jeganathan *et al.* 2015). However in the next few years, it is hoped that new treatment options will emerge for both nvAMD and atrophic AMD that will give us a menu of choices for each of our patients. This will present interesting challenges for us in

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assessing what treatment options are best for individual patients, and hopefully will lead to even better outcomes. This review summarises the data on emerging treatment options for AMD. It is not an exhaustive list, but aims to cover several specific interventions that may be mentioned in professional and popular press, and in the process illustrate the nature of studies that precede an intervention becoming available in our practices. Some relevant 'headline' interim results have not yet been published in the scientific literature, but are available in recent corporate press releases.

Please insert a brief paragraph describing what is meant by different phases of clinical studies here as it will aid the reader as they go through the rest of the paper

Neovascular age-related macular degeneration.

Anti-platelet derived growth factor agents.

Pegpleranib (Fovista®) provides an interesting and evolving case study of the development of potential new treatments. It is an antibody against platelet-derived growth factor (PDGF). Endothelial cells line blood vessels, and in the smallest blood vessels; capillaries and venules; endothelial cells are enveloped by another cell type, the pericyte. Pericytes maintain and regulate endothelial cells (van Dijk, Nieuweboer et al. 2015), and thereby microvascular health. Pegpleranib strips pericytes away, and thus was thought to facilitate the action of anti-VEGFs. Phase I and II studies are clinical trials primarily designed to investigate the safety of a drug: data on effectiveness from phase I/II studies are useful in planning of further trials, but never definitive. In a phase II study on nvAMD, participants who received ranibizumab and pegpleranib gained a mean of 10.6 letters after 24 weeks, statistically significantly better than the mean gain of 6.5 letters of those who received ranibizumab alone (Jaffe, Ciulla et al. 2016). With these encouraging results, two parallel phase 3 trials were undertaken, comparing pegpleranib and ranibizumab with ranibizumab alone (ClinicalTrials.gov Identifiers: NCT01944839 and NCT01940900). Phase III trials are designed to investigate safety and effectiveness, often being statistically powered to test a

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primary outcome measured by BCVAs. In December 2016 the year one results were reported of the phase III trials on pegpleranib (<https://www.novartis.com/news/media-releases/novartis-provides-update-pegpleranib-phase-iii-clinical-trial-program-patients>, accessed December 2016). No differences in BCVA were evident between the two arms, in each trial, and both trials have since been terminated. Thus even with positive phase II trial results, the phase III trials failed to show effectiveness, and the future of pegpleranib as a potential ophthalmic treatment is uncertain.

A different anti-PDGF was tested in the CAPELLA trial, an ongoing phase II study. Interim results were announced in a press release in September 2016 (<http://investor.regeneron.com/releasedetail.cfm?releaseid=991601>, accessed December 2016). In CAPELLA over 500 participants were randomized to receive intravitreal aflibercept and rinucumab or aflibercept alone, but at 12 weeks those receiving the combination treatment showed no benefits in terms of vision or anatomic outcomes. Further results are expected on the outcomes at week 24 and on trial completion at 52 weeks.

New Subtitle 'Tie2 Receptors'

Vascular endothelial cells have a receptor called Tie2, a target for two molecules (ligands) (Fagiani and Christofori 2013). The first ligand is angiopoietin 1 (ang-1), which has a physiological role mediating blood vessel maturation and survival. The other ligand, ang-2 contributes to angiogenesis. Angiogenesis is appropriate in some circumstances, such as during embryogenesis, tissue healing or in the menstrual cycle but clearly is pathological in other settings, such as in the aging macula or in a growing tumour. Necvasumab is a selective inhibitor of 'ang 2' that may have a therapeutic role. Necvasumab was reported as being safe when given intravenously for with solid tumours in 47 participants in a dose escalation study (Papadopoulos, Kelley et al. 2016). A trial in the US plans to recruit over 300 patients with nvAMD in an ongoing phase II study comparing intravitreal aflibercept with intravitreal necvasumab (ClinicalTrials.gov Identifier: NCT02713204).

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New Subtitle 'Targeting Different Isomers'

Not all VEGF molecules are the same: in the family of VEGF molecules, many versions of VEGF; isoforms; exist, which differ slightly in structure and function (Guyot and Pages 2015). Ranibizumab inhibits all isoforms of VEGF-A, while aflibercept inhibits multiple isoforms of VEGF-A and VEGF-B. However these two drugs do not inhibit other members of the VEGF family: VEGFs C and D. In clinical practice, cases of nvAMD are seen which respond neither to ranibizumab or aflibercept: is this because of the VEGF isoforms driving the disease in particular patients? Plasma levels of VEGF C and D have been found to be significantly associated with nvAMD (Teague GC 2016). In a mouse model of choroidal neovascularization, the extent of CNVM activity as measured by fluorescein angiography was significantly less in mice given both an intravitreal inhibitor of VEGF C and D (VGX-300) and aflibercept compared to those treated with either agent alone (Lashkari K 2015). In April 2016, no 'dose-limiting toxicities' were reported in 20 patients who had received up to 2.0mg of a 'VEGF-C/D trap therapy' (OPT-302) intravitreally. Visual gains and improvements on OCT parameters occurred to a greater degree with OPT-302 and ranibizumab than with ranibizumab alone (http://www.opthea.com/pub/pdf/ASX_OPT_OPT302%20Ph%201%20Secondary%20Endpoints_FINAL_16%2007%2026_Aust.pdf accessed Dec. 2016). An ongoing phase I/II trial is investigating OPT-302 for the treatment of nvAMD on its own compared with OPT-302 in combination with ranibizumab (ClinicalTrials.gov Identifier: NCT02543229). As described above however, as a phase I/II study the results only serve as a *suggestion* of potential efficacy: it is not guaranteed that phase III studies will confirm this.

New Subtitle 'The use of DARPins'

Designed ankyrin repeat proteins ('DARPins') are proteins of a type known as 'scaffold proteins': they usually consist of six tightly packed repeats of 30

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amino acids (the building blocks of all proteins). Some fixed amino acid positions preserve this structure, but the key is in the variable positions, which give DARPins a specific target. Being genetically engineered, the target of a DARPin can be chosen. As well as being small (and therefore in theory able to penetrate tissues), and specific (in theory limiting side effects), they are potent. A DARPin targeting VEGF-A is known as MP0112, or abicipar. In a phase 1 study in patients with DMO, a single intravitreal injection of 0.4mg of MP0112 led to half 'maximal inhibitory' concentrations in the aqueous after 12 weeks, thus suggesting the clinical effects may, in theory, be long-lived (Campochiaro, Channa et al. 2013). A phase I/II dose-escalation study suggested that MP0112 was safe and perhaps effective for nvAMD (Souied, Devin et al. 2014). For nvAMD, the 'REACH study' randomized 64 patients to one of three intravitreal treatments: 1mg abicipar (injected at baseline, 4 and 8 weeks), 2mg abicipar (injected at baseline, 4 and 8 weeks) or 0.5mg ranibizumab (injected at baseline and at 4, 8, 12 and 16 weeks), measuring outcomes at 20 weeks (http://www.molecularpartners.com/wp-content/uploads/2014/10/201407_positive_phase2_for_darpin_abicipar.pdf). Reported interim results were that the mean BCVAs at 20 weeks showed a 9.0 letter improvement for abicipar 2mg, 7.1 letters for abicipar 1mg and 4.7 letters for ranibizumab. No serious adverse events were reported: 5 in total in the abicipar groups had an 'ocular inflammatory adverse event'. Although not statistically powered for this outcome, the study confirms the merit of further trials.

New Subtitle 'Topical treatments'/other delivery methods

Topical treatments for nvAMD are at once a counterintuitive and an extremely attractive option. At face value it seems unlikely that an eye drop could be an effective option for a macular condition. Squalamine inhibits VEGF and other proangiogenic factors such as platelet-derived growth factor and basic fibroblast growth factor through a novel mechanism. It has been made up in a topical preparation that can sustain therapeutic concentrations in the posterior segment of the eye. The formulation; OHR-102 (0.2% squalamine lactate ophthalmic solution) was evaluated in a study called 'IMPACT'. In this phase II

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study, 142 patients were given intravitreal ranibizumab monthly *prn*, and were randomized to receive twice daily drops of either OHR-102 or placebo. At 9 months in the 94 of those with occult CNV of less than 10mm² area, those on ranibizumab alone gained a mean of 5.7 letters, while those on squalamine drops too gained a mean of 11.0 letters, with no difference in the number of ranibizumab injections given between the two groups. A phase III study is ongoing (ClinicalTrials.gov Identifier: NCT02727881). Another innovation that may obviate the need for patients to undergo regular intravitreal injections is being investigated in the 'LADDER' trial: a port delivery system (ClinicalTrials.gov Identifier: NCT02510794). The port is a reservoir that is implanted into the eye, but allows external access so it can be flushed out and refilled. The LADDER trial is a phase II trial in which 3 concentrations of reservoir-based ranibizumab are being evaluated, in comparison to monthly intravitreal injections. As the delivery system elutes the drug over a prolonged period of time, it is hoped that the frequency of refill may be less than monthly. Results are expected in 2018.

DRY AMD

Subtitle: Inhibiting the visual cycle

As well as these fascinating options on the horizon for nvAMD, several innovations may allow us to treat atrophic AMD. Visual cycle modulation aims to prevent RPE cell death. The principle is in effect visual cycle inhibition. Why would this be desirable? A by-product of the visual cycle is A2E, which has pathologic effects: generation of reactive oxygen intermediates, complement activation and up-regulation of VEGF. Slowing the cycle may impair photoreceptor recovery but also may reduce A2E accumulation. Fenretinide is a synthetic vitamin A derivative. Vitamin A, necessary to keep the visual cycle going, is transported from the liver to the eye by being carried on retinol binding protein. Fenretinide prevents this by attaching to retinol binding protein and ensuring excretion of the transport protein in the urine, thus ensuring less vitamin A is delivered to the eye. It has been used in trials for over 25 years on an estimated 9000 patients as a potential treatment for

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several conditions, including rheumatoid arthritis, psoriasis and cancer (Mata, Lichter et al. 2013). In these trials it was found to be safe but in general success was limited, and a side effect was delayed dark adaptation. For atrophic AMD, a phase II trial randomized 246 patients to once daily oral placebo, 100g or 300g fenretinide (Mata, Lichter et al. 2013). Delayed dark adaptation and reduced night vision, as assessed by questionnaires, was detected in approximately 40% of those receiving fenretinide but in 30% of those on placebo. Reduced GA growth rates at 2 years were seen in those on fenretinide compared to placebo *only* in those in whom the serum retinal binding protein levels were reduced to under a low threshold, and even then only a trend was observed rather than a statistically significant difference. Interestingly any clinical effects on GA were seen only after a year of treatment, suggesting that the eyes may have mechanisms to maintain vitamin A levels in times of deficiency. In contrast to the lack of apparent benefit for atrophic AMD, of note in this trial was that the incidence of CNV was significantly less in the treatment arms than the placebo arms, at approximately 20% versus 9% over 2 years. Thus fenretinide's place may lie on the menu of treatments for nvAMD.

Subtitle: 'The complement system'

The complement cascade is becoming well known to retinal specialists, given the multiplicity of genetic and pathological evidence that complement cascade overactivity is central to the pathogenesis of AMD (van Lookeren Campagne, Strauss et al. 2016). The complement cascade describes part of the innate immune system: a set of reactions in which proteins are serially activated in response to a perceived threat, such as an invading microorganism or foreign material. The resulting attack aims to neutralize the threat, but if the complement system is activated, for example by elements in drusen, collateral damage can occur. By slowing the complement cascade, complement inhibition (CI) aims to reduce collateral damage. Eculizumab is an inhibitor of C5, one of the complement proteins in the cascade. It is used for the treatment of two non-ophthalmic diseases, haemolytic uraemic syndrome and paroxysmal nocturnal haemoglobinuria. The 'COMPLETE' study enrolled 30

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patients with atrophic AMD to receive eculizumab intravenously at intervals, or placebo, for 6 months (Yehoshua, de Amorim Garcia Filho et al. 2014). However there was no difference in GA lesion growth between treatment and placebo arms, as measured using OCT. A list of possible explanations is interesting to consider (Yehoshua, de Amorim Garcia Filho et al. 2014). Systemic delivery, shown to be safe and assumed to cause adequate complement inhibition in the *choroid*, speculatively did not achieve this where it was perhaps needed, in the retina. Perhaps C5 was the wrong target, and inhibition of earlier steps of the cascade was needed. Perhaps a larger or longer study was needed, or one with a different means of measuring the outcome. It may be that complement has no role in GA growth, but another trial suggests CI is a useful approach. 'MAHALO' was a phase II trial investigating an anti-factor D drug, lampalizumab (Regillo C 2013). One hundred and twenty-nine participants with GA were randomized twice: to either intravitreal lampalizumab or sham injection, and to either monthly or bimonthly treatment. Change in atrophic AMD was measured at 18 months using autofluorescence. There was a 20.4% reduction in geographic atrophy (GA) progression in those receiving lampalizumab compared to those receiving sham. Intriguingly, in the 57% of participants who had a specific genetic change known to be associated with increased risk of AMD, in the gene *CFI*, the reduction in GA progression was 44% with lampalizumab compared to sham. While the numbers of patients in this genetic subgroup was not adequate for statistical significance to be reached, the finding brought to life the possibility of genetically testing patients to assess which treatment may be most effective for them. 'CHROMA' (ClinicalTrials.gov Identifier: NCT02247479) and 'SPECTRI' (ClinicalTrials.gov Identifier: NCT02247531) are two phase 3 trials investigating lampalizumab for atrophic AMD, aiming to recruit almost 1000 participants and expected to finish data collection in November 2018.

Subtitle 'Replacing RPE cells'

Can RPE cells, or their function, be replaced? Many approaches to replacing their function have been tried (eyewiki.aao.org/Retina_Prosthesis, accessed December 2016). One is the Argus II system (Ho, Humayun et al. 2015).

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Glasses are worn which have a small central camera. The camera collects the image and sends it to a visual processing unit (VPU), worn by the patient. The VPU down samples the information, though the user has some control over image processing, for example being able to manipulate the contrast. A transmitter coil on the side of the glasses sends information wirelessly to a receiving antenna, fixed to the sclera under the lateral rectus and a scleral band. This is attached in turn to an electrode array tacked onto the epiretinal surface at the macula. The electrodes emit pulses of electricity, the amplitude of which corresponds to the brightness of the scene at that location. The patient receives visual 'percepts', and there is a learning curve to interpret them. The Argus II trial investigated the device not on patients with AMD, but on patients with no or bare light perception due to retinitis pigmentosa (RP), but the model, or the principles behind it, may have relevance for atrophic AMD in the future. In the trial the primary efficacy outcomes were 3 computer-based visual tasks, developed with input from the low vision community: touching a white square presented at random on a black touchscreen, identifying the direction of movement of a white bar across the same screen and a grating VA assessment (Ho, Humayun et al. 2015). Thirty participants acted as their own controls by simply switching the device on or off. At 3 years, visual function in all 3 tasks improved with the device on, and other than in 1 subject in whom the device was explanted due to recurrent conjunctival erosion, all devices were technically reliable. Serious adverse events included hypotony in 4, presumed endophthalmitis in 3 (all culture negative), retinal detachment in 2, infective keratitis in 1 and a corneal melt in 1, but all were treatable. In the USA, despite the trial being small, the FDA approved the system for patients with end-stage RP, given that the degree of visual loss was profound, and that the rate of adverse events was said to be similar to that seen in glaucoma drainage devices. The 5-year results on 24 patients indicated ongoing safety and visual benefits (da Cruz, Dorn et al. 2016), and the Argus II is the only retinal prosthesis approved in the USA, Europa and Canada. Over 200 patients have had the Argus II system implanted to date.

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Subtitle 'stem cells'

Most cells in our body are specialized for specific roles: as liver cells, photoreceptors, skin cells or muscle cells for example. However all cells start with the potential, in theory, to differentiate into any cell in the body: they are pluripotent. Stem cells have this potential, and often make headlines as scientific breakthroughs are reported on their use to replace or recreate tissues. Stem cells can be found in the adult body in certain sites, such as the edge of the cornea, but can be difficult to harvest. Embryonic sources of stem cells raise ethical concerns to many. However John Gurdon and Shiya Yamanaka won the Nobel prize in medicine in 2012

(https://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/popular-medicineprize2012.pdf, accessed December 2016) for starting with mature skin cells, and 'dedifferentiating' them by adding four proteins, termed the 'Yamanaka Factors', to form 'induced pluripotent stem cells' (iPSCs). These iPSCs have the potential, in theory, to form any cell type in the body and therefore offer new hope for many diseases, including diabetes mellitus, Parkinsons disease and Alzheimers, as well as AMD. Although there are challenges to overcome in the use of iPSCs, including post-transplant survival, and limiting tumorigenicity, the remarkable discovery of this means to create an unlimited source of stem cells not only overcomes ethical objections associated with the use of embryonic stem cells, but may provide a source of cells that, once differentiated, can be transplanted without concerns about immune rejection, as they could originate from the patient due to receive the transplant. The use of iPSCs in clinics is not close, but they have been used to reliably create human RPE cells, and several trials for atrophic AMD are ongoing (Fields, Cai et al. 2016).

It is clear that there is currently a great effort in the vision science community to develop new approaches to treating both nvAMD and atrophic AMD. We live in interesting times in this regard, and as some of these and other yet unnoticed therapies become a reality for our patients, our professional practice will become ever more interesting. As patients become more informed about management options for their own conditions, it is incumbent

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on us, as optometrists and ophthalmologists, to keep at least as up to date as our patients. We will need to be able to translate and temper information publically available online and in the popular press and to recommend the best treatment for the individual in front of us.

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